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Genetic risk for bipolar disorder and psychopathology from childhood to early
adulthood

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Abstract

Background

Studying the phenotypic manifestations of increased genetic liability for Bipolar Disorder (BD) can increase understanding of this disorder.

Aims

We assessed whether genetic risk for BD was associated with childhood psychopathology and features of hypomania in young adulthood within a large population-based birth cohort.

Methods

We used data from the second Psychiatric Genetics Consortium Genome Wide Association Study (GWAS) for Bipolar Disorder to construct a polygenic risk score (PRS) for each individual in the Avon Longitudinal Study of Parents and Children (ALSPAC). Linear and logistic regression models were used to assess associations between the BD-PRS and emotional/behavioural difficulties, attention deficit hyperactivity disorder (ADHD) and borderline personality disorder (BPD) traits in childhood, as well as hypomania in early adulthood (sample sizes from 2,654 to 6,111).

Results

The BD-PRS was not associated with total hypomania score, but was weakly associated with a binary measure of hypomania (OR=1.13, 95%CI 0.98,1.32; $p=0.097$), and particularly at higher hypomania symptom thresholds (strongest evidence OR=1.33, 95%CI 1.07, 1.65; $p=0.01$). The BD-PRS was also associated with ADHD (OR=1.31, 95%CI 1.10, 1.57; $p=0.018$), but not with other childhood psychopathology.

Limitations

The PRS only captures common genetic variation and currently explains a relatively small proportion of the variance for BD.

Conclusions

The BD-PRS was associated with ADHD in childhood, and weakly with adult hypomania, but not with other psychopathology examined. Our findings suggest that genetic risk for BD does not appear to manifest in childhood to the same extent as schizophrenia genetic risk has been reported to do.

Key words ALSPAC, ADHD, Polygenic Risk Score, Bipolar Disorder, Hypomania

1. Introduction

Bipolar disorder (BD) is a common psychiatric disorder (Cross-Disorder Group of the Psychiatric Genomics, 2013) with a lifetime risk of 1-2% (Merikangas et al., 2011). Difficulties in accurate diagnosis during the early course of BD contribute to a substantial illness burden to the individual and society (Connell et al., 2012; Marwaha et al., 2013; Park et al., 2013).

Hypomanic/manic episodes that are required for a diagnosis of BD rarely manifest before age 25 years (Leboyer et al., 2005), although depressive episodes frequently precede these, and sometimes by as much as 10 years before a diagnosis of BD, rather than unipolar depression, becomes apparent (Fritz et al., 2017). Individuals with BD often have a history of psychopathology in childhood/adolescence that is broader than just depression (Duffy et al., 2010; Topor et al., 2013). For example, Attention Deficit Hyperactivity Disorder (ADHD), conduct problems and hyperactivity in childhood have been associated with a greater risk for developing BD (Donfrancesco et al., 2011; Henin et al., 2007; Singh et al., 2014). Borderline personality disorder (BPD) has also been associated with increased risk for developing BD, and is often present co-morbidly in adults with BD (Fornaro et al., 2016; Parker et al., 2016). Furthermore, whilst manic episodes rarely occur before young adulthood, sub-threshold hypomanic symptoms may occur much earlier than the first diagnosis of BD and may be useful for predicting both BD onset (Fiedorowicz et al., 2011) and conversion from depression to BD (Tijssen et al., 2010).

Whilst the phenomenological overlap and high rates of comorbidity between the psychopathology described above and BD may be due to shared genetic heritability (Cross-Disorder Group of the Psychiatric Genomics, 2013; Witt et al., 2017), it is currently not known how genetic risk for BD manifests during childhood, adolescence, and early adulthood in the general population (Mistry et al., 2018). Understanding this is important as it could help inform the identification of individuals who are most at risk of developing BD, and minimise misdiagnosis and incorrect treatment (Ghaemi et al., 1995; Hirschfeld and Vornik, 2004; Keck et al., 2008).

BD has a heritability of approximately 60-85% (Craddock and Sklar, 2013). and Genome Wide Association Studies (GWASs) have identified a number of single nucleotide polymorphisms (SNPs) that occur more frequently in BD cases relative to controls (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genetics Consortia, 2018; Cross-Disorder Group of the Psychiatric Genomics, 2013; Sklar et al., 2011; Stahl et al., 2017). One method to examine the effect of multiple SNPs on disease risk is the polygenic risk score (PRS) approach, which provides biologically valid indicators of disease risk for research (Cross-Disorder Group of the Psychiatric Genomics, 2013; Purcell et al., 2009). Although individual risk SNPs have small effects on disease risk, taken together alleles on current GWAS platforms explain approximately 4% of the genetic variation for BD on the liability scale (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genetics Consortia, 2018; Cross-Disorder Group of the Psychiatric Genomics, 2013; Ikeda et al., 2017; Stahl et al., 2017).

In this study we therefore used the polygenic risk score (PRS) approach to assess whether genetic risk for BD, calculated using the largest GWAS on BD to date (Stahl et al., 2017), was associated with childhood psychopathology or features of hypomania assessed in early adulthood within a large, population-based birth cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC).

2. Methods

2.1 Participants

ALSPAC (www.bris.ac.uk/alspac/) was set up in April 1991. Mothers of children born in the South West of England (Avon) between 1st April 1991 and 31st December 1992 (Boyd et al., 2013) were invited to take part. The initial cohort contained 15,445 participants (Boyd et al., 2013) with extensive baseline information from the first trimester of pregnancy onwards. Data were collected regularly at defined time intervals and is ongoing. The study website contains details of all the data, searchable through the data dictionary (www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). This study received ethical approval from the ALSAPC Law and Ethics Committee and Local Research Ethics Committees (<http://www.bristol.ac.uk/alspac/researchers/research-ethics/>).

2.2 Hypomania

When the cohort were 22-23 years of age, postal and online questionnaires for assessing lifetime history of hypomanic symptoms, using the Hypomania Checklist-32 (HCL-32) were sent. In total, 9,359 participants were invited to complete the HCL-32, of whom 3,448 (37%) returned the questionnaire. The HCL-32 has been used extensively in clinical and non-clinical settings and is validated as a screening tool for BD type II (Angst et al., 2011; Forty et al., 2009; Holtmann et al., 2009; Meyer et al., 2014).

A previous study conducted a Rasch analysis for unidimensionality of the HCL-32 and identified four items as redundant and could be excluded (Court et al., 2014). Therefore, in our study, we have used these 28 items to derive our outcomes:

- i) Hypomania symptom score: Our primary outcome of hypomania that reflected the total HCL score (range 0 to 28), which was then standardised.

- ii) Hypomania: Our secondary outcome of hypomania was a binary outcome defined as meeting a threshold score on the HCL of $\geq 14/28$, in addition to having symptoms for a duration of 2-3 days or more (to satisfy the ICD-10 criteria for hypomania to have lasted for “at least several days”), and a response of either negative, or both negative and positive impact of highs on family life, social life, work life or leisure. Whilst a score of $\geq 14/28$ yields the best sensitivity and specificity in clinical samples (Fornaro et al., 2015; Mosolov et al., 2014; Perugi et al., 2012; Wu et al., 2008), higher threshold cut off scores, indexing a greater degree of psychopathology, will likely capture individuals who are most likely to have ‘clinically-relevant’ hypomania. We therefore also examined, as sensitivity analyses, binary measures of hypomania defined by HCL scores of $\geq 16/28$, $\geq 18/28$, $\geq 20/28$, $\geq 22/28$ and $\geq 24/28$ to explore whether results are consistent irrespective of how we define the outcome, and if not, how they change as we alter the cut-off threshold
- iii) Hypomania factors: Other secondary outcomes were latent factors relating to a) ‘energy/mood’ and b) ‘risk-taking/irritability’ that have previously been derived (An et al., 2011; Fornaro et al., 2015; Hantouche et al., 2003; Meyer et al., 2007), and confirmed in this sample (Mistry et al., 2017).

2.3 Emotional and behavioural difficulties

We used the Strengths and Difficulties Questionnaire (SDQ) that was completed by parents when their children were aged 9 years as a measure of emotional and behavioural difficulties (Goodman, 1997). We examined associations between the PRS and the SDQ total difficulties score (which was standardised), and, as secondary analyses, with scores for the 5 SDQ subscales (hyperactivity problems, prosocial behaviour, emotional difficulties, conduct problems and peer relationship difficulties), in a sample of 6,111 children.

2.4 Assessment of childhood ADHD

At age 91 months (7.6 years), the presence of ADHD was assessed in 8,219 children using the Development and Wellbeing Assessment (DAWBA), based on parent ratings (Goodman et al., 2000). This assessed the presence of psychiatric disorders including DSM-IV ADHD, rated as absent or present. Whilst presence of any ADHD sub-type (inattentive, hyperactive-impulsive, or combined) was our primary outcome, we also examined as a secondary analysis whether associations were stronger for one sub-type compared to another.

2.5 Assessment of borderline personality disorder (BPD) traits

At age 11 years, the cohort was interviewed to assess their experience of BPD traits over the preceding two years. The interview was conducted by trained psychologists, using the Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD). This is a semi-structured interview designed to assess BPD traits in latency-age children and adolescents, adapted for use in this cohort (Zanarini et al., 2004). The CI-BPD is based on the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (Zanarini et al., 1996). The convergent validity of the CI-BPD has been shown by findings that this measure is significantly associated with clinician diagnosis and other measures of BPD reported by patients and parents (Sharp et al., 2012). It contains nine BPD traits (anger symptoms, affective instability, emptiness, identity disturbance, paranoid ideation, abandonment, suicidal behaviour, impulsivity and intense interpersonal relationships). Judgements were made by a trained assessor and rated as absent, probably present or definitely present (coded as 0, 1 and 2 respectively). To meet criteria for definitely present, the trait had to be present at least 25% of the time (or daily). A probably rating required the trait to be present regularly but not as often as definitely.

We derived a BPD traits score by summing the 9 individual BPD traits (range from 0-18) and standardised this score. Furthermore, individuals in the present study were classified as being 'high risk for borderline personality disorder' if they were rated

‘probably’ or ‘definitely’ on 5 or more of the nine items, as used previously (Wolke et al., 2012).

2.6 Genetics

Genetic data from 9,912 participants were obtained using the genome wide single-nucleotide polymorphism genotyping platform (HumanHap550-Quad; Illumina). GWAS data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Following quality control, imputation, and restriction to 1 young person per family, genetic data were available on 8,230 individuals (see Supplementary methods available online for more detail).

Prior to construction of the PRS, SNPs were removed from the analysis if their imputation quality (INFO) score was <0.8 , had a minor allele frequency (MAF) of <0.01 or if there was a mismatch of alleles between the PGC and ALSPAC.

2.7 Polygenic Risk Scores (PRS)

The PRS for BD was constructed using summary statistics from the second Psychiatric Genetics Consortium Bipolar Disorder (PGC-BD) Genome Wide Association Study (GWAS) (Stahl et al., 2017). The PGC study, containing information on risk alleles and their corresponding effect sizes, was used to generate a PRS for each individual in ALSPAC.

SNPs were clumped using PLINK v1.90 using the `--clump` command. The PRS was derived using $r^2 < 0.2$ within 1MB windows, and using SNPs with a $P_T \leq 0.5$ (Sklar et al., 2011) (our primary exposure threshold for all outcomes), and additionally a $P_T \leq 0.01$ (the threshold that maximally captures BD liability) (Stahl et al., 2017) for our hypomania outcomes.

The PRS for each individual in ALSPAC was calculated using the `--score` command on PLINK. To generate the score, the sum of the total number of risk alleles present

for each SNP (0, 1, 2) was weighted by the log of its odds ratio (OR) for BD from the PGC. The ALSPAC sample has been shown to have no significant population stratification, and genome-wide analyses of phenotypes indicate a low λ (Martin et al., 2015; Zammit et al., 2014). Therefore, we did not adjust for population stratification using principle components analysis.

2.8 Statistics

Logistic regression was used to determine associations between the BD-PRS and hypomania, ADHD and being 'high-risk' for borderline personality disorder. These results are presented as odds ratios (ORs) per standard deviation (SD) increase in PRS. Linear regression was used to determine associations between the BD-PRS and hypomania symptoms score, hypomania latent factors, SDQ scores and borderline personality disorder traits score. These results are presented as SD change in outcome per SD increase in PRS. R^2 values (and Naglekarke r^2 for logistic) are reported as a measure of the variance in outcome explained by the PRS. Data were analyzed using STATA statistical software ([version 14.1](#) [SE](#), [College Station, TX](#): StataCorp LP).

3. Results

3.1 Sample characteristics

Of the 8,230 ALSAPC individuals whose genetic data passed quality control checks (51.2% male), 2,654 to 6,111 participated in the assessments used from age 7 to 23 years (Table 1).

Insert Table 1

3.2 BD-PRS and hypomania

The BD-PRS was not associated with higher hypomania symptom scores ($p=0.336$). However, there was very weak evidence the BD-PRS was associated with increased odds of being classified as having hypomania at the threshold cut off score of $\geq 14/28$ (OR=1.13, 95%CI 0.98, 1.32; $p=0.097$) at $P_T \leq 0.5$ (Table 2).

Insert Table 2

When using higher threshold cut-off scores on the HCL to define hypomania, we found stronger evidence that a higher BD-PRS was associated with increased odds of having hypomania, with strongest evidence at an HCL score cut-off threshold of $\geq 20/28$ (OR=1.33, 95%CI 1.07, 1.65; $p=0.01$) (Supplementary Table 1).

The BD-PRS was not associated with either the ‘energy/mood’ ($p=0.292$), or ‘risk-taking/irritability’ factors ($p=0.572$) (Table 2).

Evidence of association with hypomania symptom scores, hypomania factors, and hypomania at the threshold cut off score of $\geq 14/28$ was weaker at a P_T of ≤ 0.01 , whereas the association with hypomania at the threshold cut off score of $\geq 20/28$ was very similar to that for $P_T \leq 0.5$ (Supplementary Tables 2 & 3).

3.3 BD-PRS and other psychopathology

There was strong evidence that the BD-PRS was associated with increased odds of being diagnosed with ADHD (OR=1.31, 95%CI 1.10, 1.57; $p=0.003$) (Table 3).

Additionally, we were interested in whether associations were more strongly associated with a specific type of ADHD. We found evidence of association with inattentive ADHD (OR=1.37, 95%CI 1.06, 1.79; $p=0.018$), but not hyperactive-

impulsive or combined ADHD, though confidence intervals for all subtypes overlapped substantially (Supplementary Table 4).

We found no evidence the BD-PRS was associated with the SDQ total difficulties score ($p=0.302$), nor with the individual SDQ subscales: hyperactivity ($p=0.760$), prosocial behaviour ($p=0.951$), emotional difficulties ($p=0.175$), conduct problems ($p=0.131$) and peer relationship difficulties ($p=0.231$) (Table 3).

There was no evidence of association between the BD-PRS and the BPD traits score ($p=0.898$) and similarly no evidence of an association between the BD-PRS and being classed as 'high-risk' for borderline personality disorder ($p=0.860$) (Table 3).

Insert Table 3

4. Discussion

4.1 Summary of findings

Within this large population-based birth cohort, we found no evidence of association between the BD-PRS and hypomania symptom score or the hypomania factors.

There was [very](#) weak evidence of association between the BD-PRS and a binary measure of hypomania, though evidence was stronger when greater symptom number counts were required to be classed as having hypomania.

There was strong evidence of an association between the BD-PRS and ADHD, but no evidence for association with SDQ scores, BPD traits score or being 'high-risk' for BPD.

4.2 Findings in the context of previous work

4.2.1 BD-PRS and hypomania

We are unaware of previous studies examining genetic risk for bipolar disorder and hypomania as an outcome per se. Two studies have examined whether the BD-PRS can discriminate those with BD-I compared to those with BD-II, though these studies reported inconsistent results (Aminoff et al., 2015; Charney et al., 2017).

The BD-PRS is derived from a GWAS of clinical samples of individuals with bipolar disorder (Sklar et al., 2011; Stahl et al., 2017), who would have more severe psychopathology than those who meet criteria for hypomania in our sample. This may explain why evidence of association with hypomania in our study was weaker than for studies that have reported the ability of the BD-PRS to predict BD case status in clinical samples (Charney et al., 2017; Power et al., 2015; Schulze et al., 2014; Tesli et al., 2014). [Whilst we did find evidence of association with hypomania in our sensitivity analysis, this needs to be interpreted in the context of testing a number of hypomania outcomes defined at different score thresholds. Overall](#)

therefore, our findings suggest that measures of hypomania in the young adult general population do not strongly reflect the influence of genetic risk for BD.

4.2.2 BD-PRS and SDQ

We have previously shown that the SDQ subscales for hyperactivity and conduct problems are associated with “dark-side” hypomania (Hantouche et al., 2003) as indexed by the ‘risk-taking/irritability’ factor in our study (Mistry et al., 2017). We therefore expected the BD-PRS to be associated with the SDQ, but this was not the case. A possible reason for our lack of finding associations between genetic risk for BD and the SDQ might be related to the completion of the SDQ by the parents. It is possible the behavioural problems the children were experiencing may have been underestimated by some of the parents, which could lead to greater measurement error. This could result in associations being relatively underpowered for this phenotype, though the SDQ is a well validated measure of childhood psychopathology (Goodman, 1997). It is also possible that genetic risk for BD is not expressed as any of the broad range of psychopathologies measured by the SDQ.

To our knowledge, only one other study has examined whether genetic risk for BD is associated with childhood psychopathology. Using data from the Generation R cohort, the authors reported the BD-PRS (using the PGC-1-BD GWAS summary statistics) was not associated with externalising or internalising scales on the Child Behaviour Checklist (CBCL) in children at ages 3, 6 and 10 years (Jansen et al., 2018). Our study, though the first to examine the association of childhood psychopathology with the most recent PGC-2-GWAS of BD is consistent with these findings.

4.2.3 BD-PRS and ADHD

Comorbidity between ADHD and BD along with symptom overlap between these disorders has been well documented (Singh et al., 2006). Age of onset of diagnosed BD (Sachs et al., 2000) and first presentation of affective symptoms (Ryden et al., 2009) are significantly earlier in those who have a history of childhood ADHD

compared to those without childhood ADHD. However, a narrative review of prospective cohort studies of the offspring of parents with BD reported that a clinical diagnosis of childhood ADHD was not a reliable predictor of future development of BD (Duffy, 2012), although the studies included in this review (9 in total) had low numbers of participants within each study (7 – 216 individuals). We have previously shown that a diagnosis of ADHD was associated with the ‘risk-taking/irritability’ factor of hypomania, though this association may not be with bipolar disorder per se (Mistry et al., 2017).

Our findings are consistent with several studies reporting the BD-PRSs ability to discriminate ADHD cases from controls (Hamshere et al., 2013; Schimmelmann et al., 2013). However, it is important to acknowledge the extent of shared genetic heritability between BD and ADHD is small, evidenced by a relatively small proportion of the variance in ADHD explained by the BD-PRS (Cross-Disorder Group of the Psychiatric Genomics, 2013). Our study suggests that genetic risk for BD might manifest more as inattention rather than hyperactivity/impulsivity in childhood, although our findings are also compatible with similar effect sizes for the different ADHD subtypes. There is some evidence that symptoms of hyperactivity and impulsivity tend to decline with age whilst inattention typically persists (Faraone et al., 2015), and our findings might therefore reflect a greater genetic (including cross-disorder) contribution to the inattentive ADHD subtype.

Our finding of stronger evidence of association between genetic risk for bipolar disorder and ADHD, compared to genetic risk for BD and hypomania, could be the result of how these measures were assessed in the ALSPAC cohort. ADHD was assessed using the DAWBA, a questionnaire completed by the parents, whilst the HCL-32 was a self-report questionnaire. ADHD diagnosis was based on DSM-IV criteria whilst our measure of hypomania in this study is based on a symptom score threshold with evidence of impaired function, so is more loosely related to DSM-IV criteria for bipolar II disorder. It is possible that the DAWBA is a more accurate measure of assessing for ADHD than the HCL-32 is for assessing hypomania, and that measurement error for the latter is greater. The weak evidence overall of association between high genetic risk for BD and our binary measures of hypomania

[suggests the HCL does not accurately index individuals with high propensity to developing BD.](#)

4.2.4 BD-PRS and BPD traits

At the present time, genetic research on BPD is limited. These mainly focus on candidate genes and involve small sample sizes (Calati et al., 2013). A case-control study examined the association between BD risk variants and BPD case status, and reported a weak association between the SNP rs1006737 in *CACNA1C* and BPD (Witt et al., 2014). More recently, Witt et al., (2017) conducted the first GWAS of borderline personality disorder and found evidence of genetic overlap (genetic correlation of 0.28) between the BD-PRS and BPD (Witt et al., 2017).

We did not find evidence of a higher BD-PRS in individuals with higher BPD traits scores, or in those classed as ‘high-risk’ for BPD. Our measure of BPD traits in this sample is likely to capture a much less severe phenotype than that present in cases from the GWAS by Witt et al (2017) (Witt et al., 2017). Furthermore, whilst we defined a group of children at age 11 years as being ‘high-risk’ for borderline personality disorder, a reliable diagnosis of BPD at this age is not possible and we had no data to determine how many of these individuals who were classed as ‘high-risk’ would eventually meet criteria for this diagnosis in adulthood. This might explain the apparent inconsistency of our findings with those from Witt et al., (2017), though our results nevertheless indicate that borderline personality disorder traits in childhood are not manifest as a consequence of high genetic risk for BD. These results also suggest that associations between BPD traits in childhood and adult hypomania, as we reported recently (Mistry et al., 2017) is unlikely to be confounded by shared genetic effects, and might perhaps be more likely explained by shared environmental risk such as childhood trauma (McDermid et al., 2015).

4.3 Strengths and limitations

Our study has a number of strengths. Firstly, we used the largest and most recent Bipolar Disorder GWAS from the PGC as the training set (PGC-2-BD) (Stahl et al.,

2017), thus minimising measurement error. Second, we used a large, well characterised population-based sample for assessing our phenotypes of interest. All phenotypes, excluding hypomania outcomes, were assessed in childhood, at an age where it might be most useful to detect early manifestations of bipolar disorder. Third, we used well validated measures to assess our phenotypes, making information bias in our results less likely.

However, there are also a number of limitations. Firstly, scores on the HCL do not reflect a DSM-IV/ICD-10 diagnosis of BD. However, the score may be used to assess propensity to BD, particularly in a group of individuals where first onset of manic symptoms is unlikely to have occurred at age 22/23 years (Leboyer et al., 2005). Missing data in our sample could lead to selection bias. Whilst sample representativeness is critical for estimating prevalence, empirical and simulation studies have demonstrated that selection bias does not usually affect interpretation of results of associations between exposures and outcomes (Howe et al., 2013; Pizzi et al., 2011; Wolke et al., 2009), though we cannot be certain that our results are not affected by the extent of missing data (Ebrahim and Smith, 2013).

Finally, whilst GWAS capture effects on risk conferred by common variants, they are unable to detect effects of rare variants, thus our results reflect only common variant influences on childhood/young adulthood outcomes.

4.4 Conclusions

Within this large, prospective population-based birth cohort, we found associations between increased genetic risk for bipolar disorder and increased odds of ADHD and less robustly with hypomania, but not with other psychopathology.

Genetic risk for BD might not be manifest until later in development (in contrast to schizophrenia genetic risk where there is evidence of association with childhood psychopathology) (Nivard et al., 2017).

Further work in large, population-based longitudinal studies could explore whether phenotypic expression of genetic risk for bipolar disorder changes with age, and determine the utility of combining polygenic risk scores with other measures, such as presence of childhood psychopathology, for predicting risk of developing bipolar disorder.

Insert Supplementary Tables 1, 2, 3 and 4

Declaration of interest: none

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Insert Supplementary Tables 1, 2 and 3

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